Remarks

For the Examiner's convenience, Applicants have provided a complete listing of the claims. No amendments have been made to the claims. In view of the following remarks, reconsideration and withdrawal of the rejection is respectfully requested. Applicants believe that the application is now in condition for allowance.

Rejection Under 35 U.S.C. § 103

The Office Action mailed March 21, 2006 rejected all of the claims under examination (12-17 and 19) under 35 U.S.C. § 103(a) as being obvious over Baker et al. (US Patent No. 5,441,955; "Baker"). This rejection is respectfully traversed.

The Office Action states that Baker describes tryptanthrin compounds as part of an antimicrobial composition and that the tryptanthrin compound can be administered in combination with an adjuvant. (Office Action of March 21, 2006 at page 3). The Office Action also states that Baker teaches that tryptanthrin can be administered in combination with "one or more other agents used in the treatment of mycobacterial infections." (Id.) The Office Action next notes that BCG is a vaccine against tuberculosis caused by mycobacterial infections. The Office Action then goes on to assert that a combination of a tryptanthrin compound with an adjuvant was obvious, because "[o]ne would have been motivated to make this combination because of the increased antigenic response of the **tryptanthrin** compound resulting from the **adjuvant**." *Id.*, emphases added) The Office Action goes on to assert that adjuvants are defined as "the agents that are used for the treatment of mycobacterial tuberculosis." (Id). As discussed in more detail below, Applicants traverse the rejection and the arguments underlying the rejection. In particular, Applicants disagree with the assertion that the adjuvants described in Baker are the agents that are used for treatment of mycobacterial tuberculosis. Applicants also disagree with any possible assertion that BCG as described in Baker is an "other agent" that can be used in combination with tryptanthrin compounds.

Applicants thank the Examiner for the courtesy of conducting the interview in the above matter in April 20, 2006. In response to the Interview Summary, Applicants wish to re-assert that the basis for the lack of obviousness of the pending claims is indeed based in part at least on the fact that there is no motivation in the cited reference to

combine BCG with tryptanthrin. Furthermore, Applicants again assert that there is no motivation in Baker to use BCG as an adjuvant and thus there is no motivation to combine BCG with tryptanthrin.

Applicants respectfully traverse the Examiners rejection of the claims and the reasoning provided in support of the rejections.

The claimed compositions use tryptanthrin in combination with an antigen and Baker teaches a combination of trytanthrin with (1) an adjuvant or (2) 'other anti-*Mycobacterium tuberculosis* agents' (Column 3, lines 64 to 65). BCG as disclosed in Baker is neither (1) an adjuvant nor (2) an antimicrobial agent that would be combined with tryptanthrin. Thus, one aspect of the Applicants arguments is that a combination of BCG vaccine with a tryptanthrin is not obvious in view of Baker.

The Office Action asserts that a person of ordinary skill would have been motivated to make the combination of tryptanthrin with BCG because of the increased response of the tryptanthrin compound resulting from the adjuvant. The Examiner goes on to assert that "the adjuvant...is defined as the agents that are used for the treatment of mycotuberculosis." (Office Action of March 21, 2006 at page 3, last paragraph; S*ee also* Office Action date October 14, 2005, first paragraph, where the same assertion is made)

Assuming that Baker indeed teaches the possibility of combining tryptanthrin with "other agents," the other agents are limited to the following: (1) other anti-*Mycobacterial tuberculosis* agents (at Column 3, lines 63 to 68) and (2) pharmaceutically acceptable carriers, adjuvants and vehicles.

Baker states that the other anti-Mycobacterium tuberculosis agent can be isoniazid, rifampin, pyrazinamide, rifabutin, streptomycin and or ciprofloxacin (Column 3, lines 62 to 57). The only mention of BCG in Baker is in the background, where it is noted that BCG is a vaccine that protects against severe tuberculosis and disseminated TB in children. Applicants also note that this passage is the only mention of a vaccine in the reference. Baker **does not** teach or suggest that BCG is an "other anti-*Mycobacterium tuberculosis* agent" that can or should be combined with tryptanthrin.

Baker discloses at Column 12, lines 37 to 42, the use of adjuvants, carriers and vehicles with the tryptanthrins of the invention. Baker also states that the tryptanthrin can be combined with adjuvants, as noted above and at Column 13, lines 15 to 18 ["s]uch

compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents." Baker **does not** teach or suggest that BCG is an "adjuvant" to be combined with tryptanthrin.

To summarize, Baker teaches the combination of tryptanthrins with (1) other anti-*Mycobacterium tuberculosis* agents or (2) adjuvants. The claims are directed to a combination of a tryptanthrin with an **antigen**. An antigen is not an adjuvant nor another anti-*Mycobacterium tuburculosis* agent as described in Baker.

Even assuming for arguments sake that Baker taught the general concept of combining various agents for use in the treatment of mycotuberculosis with tryptanthrin, BCG would not be an "agent" that one would combine with tryptanthrin for treatment of TB.

First, it is noted in the Examples of Baker that the tryptanthrins inhibit growth of mycobacteria. Second, claim 8 of Baker teaches a method of inhibiting growth of mycobacteria by contacting the bacteria with a tryptanthrin compound.

In contrast, BCG is a live attenuated vaccine, which relies on multiplication of the bacteria for its effect. BCG is a vaccine made up of a live strain of *Mycobacterium*. (See *Vaccines, Fourth Edition,*2004 Eselvier Inc. [edited by S. Plotkin, W. Orenstein with assistance of P. Offit] Chapter 1, page 5, last full paragraph; Attached hereto as part of Appendix I). When administered, the live vaccine stimulates the immune system to produce antibodies against M*ycobacterium tuberculosis* bacteria. This provides immunity to protect against tuberculosis infection.

Live vaccines require **multiplication** and growth in the recipient (See *Vaccines, Fourth Edition,*2004 Eselvier Inc. [edited by S. Plotkin, W. Orenstein with assistance of P. Offit] at Chapter 8, page 110, first full paragraph; Attached hereto as part of Appendix I). In direct contrast to multiplication and growth, the tryptanthrin compounds in Baker are taught to be "useful in vitro **in inhibiting the growth** of pathogenic mycobacteria, and in vivo in human and animal hosts for treating pathogenic mycobacterial infections, including tuberculosis." (Baker, Column 12, lines 14-19; *emphasis added*).

Combining a tryptanthrin compound as described and taught in Baker with BCG would presumably inhibit multiplication and growth of the BCG vaccine and therefore

diminish or eliminate BCG's ability to produce immunity against *Mycobacterial* infections.

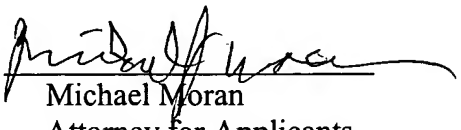
According to § 2142 of the M.P.E.P., the following three criteria must be met to establish a *prima facie* case of obviousness: (1) there must be motivation to modify the reference or combine teachings; (2) there must be a reasonable expectation of success; and (3) the reference (or combination thereof) must teach or suggest all the claim limitations. As noted above, Baker does not teach, suggest, or provide any motivation to make a pharmaceutical composition comprising a tryptanthrin compound and an antigen. Subsequently, a *prima facie* case of obviousness has not been met and the rejection should be withdrawn.

Conclusions

In view of the amendment and above remarks, it is respectfully submitted that all rejections and objections have been addressed and have been overcome. Early notice to this effect is solicited. The Examiner is cordially invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issuance.

Respectfully Submitted,

Date: September 21, 2006

By: 

Michael Moran
Attorney for Applicants
Reg. No. 42,013

NOVARTIS VACCINES AND DIAGNOSTICS
Intellectual Property Dept.
4560 Horton Street
Emeryville, CA 94608-2916
Telephone: (510) 923-2969
Facsimile: (510) 655-3542

APPENDIX I

FOURTH • EDITION

Vaccines

Stanley A. Plotkin, M.D.
Emeritus Professor of Pediatrics, University of Pennsylvania
Emeritus Professor, Wistar Institute
Adjunct Professor of International Health, Johns Hopkins University
Former Chief, Division of Infectious Diseases
The Children's Hospital
Philadelphia, Pennsylvania
Former Medical and Scientific Director, Mérieux Connaught, Paris, France
Medical and Scientific Consultant, Aventis Pasteur

Walter A. Orenstein, M.D.
Assistant Surgeon General, United States Public Health Service
Director, National Immunization Program
Centers for Disease Control and Prevention
Atlanta, Georgia

with assistance of

Paul A. Offit, M.D.
Chief, Section of Infectious Diseases
Professor of Pediatrics
The University of Pennsylvania School of Medicine
Henle Professor of Immunologic and Infectious Diseases
The Children's Hospital
Philadelphia, Pennsylvania

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NOTICE

Infectious Disease is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the licensed prescriber, relying on experience and knowledge of the patient, to determine dosages and the best treatment for each individual patient. Neither the publisher nor the author assumes any liability for any injury and/or damage to persons or property arising from this publication.

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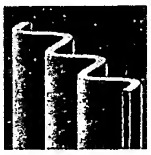
Chapter 1

A Short History of Vaccination

SUSAN L. PLOTKIN • STANLEY A. PLOTKIN



Vaccination as a deliberate attempt to protect humans against disease has a long history, although only in the 20th century did the practice flower into the routine vaccination of large populations. During the past 200 years, since the time of Edward Jenner (Fig. 1–1), vaccination has controlled the following 10 major diseases, at least in parts of the world: smallpox, diphtheria, tetanus, yellow fever, pertussis, *Haemophilus influenzae* type b disease, poliomyelitis, measles, mumps, and rubella. In the case of smallpox, the dream of eradication has been fulfilled, because this disease—at least naturally occurring disease—has disappeared from the world.[1] Poliomyelitis is targeted by the World Health Organization for eradication by the year 2005. Vaccinations against influenza, hepatitis A, hepatitis B, varicella, pneumococcal and meningococcal infections have made major headway against those diseases, although much remains to be done.

The impact of vaccination on the health of the world's peoples is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth.

Early Developments

Attempts to vaccinate did not begin with Edward Jenner. In the seventh century, some Indian Buddhists drank snake venom in an attempt to become immune to its effect. They may have been inducing toxoid-like immunity.[2] Writings citing the use of inoculation and variolation in 10th-century China[3–5] make interesting reading but apparently cannot be verified.[6] There is, however, 18th-century documentation of variolation in China with reference to its use in the late 17th century. A Chinese medical text printed in 1742, *The Golden Mirror of Medicine*, listed four forms of inoculation against smallpox practiced in China at least since 1695: (1) the nose plugged with powdered scabs laid on cotton wool, (2) powdered scabs blown into the nose, (3) the undergarments of an infected child put on a healthy child for several days, and (4) a piece of cotton smeared with the contents of a vesicle and stuffed into the nose.[3,6] Another text on Chinese medicine, published a century before Jenner's work, stated that white cow fleas were used for smallpox prevention.[4] The fleas were ground into powder and made into pills, which may have been the first attempt at an oral vaccine.

Variolation, the introduction of dried pus from smallpox pustules into the skin of the patient, was practiced at regular intervals by the Brahmin caste of Hindus in India in the 16th century. Some claim that a description of variolation can be found in the *Atharva Veda* (a pre-Hindu Indian religious text circa 1000 BC), but this is probably exaggerated enthusiasm.[7] Vaccination for smallpox with cowpox did not

FIGURE 1–1 • Edward Jenner. (Photo courtesy of the Institute of the History of Medicine, The Johns Hopkins University, Baltimore, MD.)

TABLE 1–1 ▪ Outline of the Development of Human Vaccines

Live, Attenuated	Killed Whole Organism	Protein or Polysaccharide	Genetically Engineered
18TH CENTURY			
Smallpox (1798)			
19TH CENTURY			
Rabies (1885)	Typhoid (1896) Cholera (1896) Plague (1897)		
EARLY 20TH CENTURY			
Tuberculosis (1927) (Bacille Calmette-Guérin) Yellow fever (1935)	Pertussis (1926) (whole cell) Influenza (1936) Rickettsia (1938) (typhus)	Diphtheria (1923)* Tetanus (1927)*	
AFTER WORLD WAR II			
Polio (oral) Measles Mumps Rubella Adenovirus Typhoid (salmonella Ty21a) Varicella Rotavirus (reassortants) Cold-Adapted Influenza (CAIV)	Polio (injected) Rabies (cell culture) Japanese encephalitis Tick-borne encephalitis Hepatitis A Cholera	Pneumococcus† Meningococcus† *Haemophilus influenzae* PRP† Pneumococcal conjugate‡ Meningococcal conjugate‡ *H. influenzae* PRP-conjugate‡ Hepatitis B (plasma derived)* Typhoid (Vi)† Acellular pertussis* Anthrax§	Hepatitis B recombinant (yeast or mamallian cell derived) Acellular pertussis (some components) Lyme (*Escherichia coli* recombinant)

*Purified proteins.
§Extracted proteins from whole organisms.
†Capsular polysaccharides.
‡Capsular polysaccharides conjugated to carrier proteins.
PRP, polyribosylribitol phosphate.

showed the presence of powerful antitoxins in the serum of animals previously infected with low doses of diphtheria bacilli.[54,55] The antitoxin neutralized diphtheria toxin in culture. Further experiments showed that the antitoxin provided protection in animals against challenge with the diphtheria bacillus itself. Progress occurred so rapidly after von Behring's discovery that the first child was treated with diphtheria antitoxin just 1 year later, in December 1891. Shortly thereafter, commercial production of diphtheria antitoxin began.

In the early 20th century, the chemical inactivation of diphtheria and other bacterial toxins led to the development of the first toxoids: diphtheria and tetanus. Here also Theobald Smith played a significant role. In 1907, he determined that "toxoids" provided immunity in guinea pigs. In 1909, reporting on long-lasting immunity against diphtheria in guinea pigs immunized with toxoid, he suggested that the method of making toxoids "invites further regard to its ultimate applicability to the human body."[31,56]

In 1923, Alexander Glenny and Barbara Hopkins showed that diphtheria toxin could be transformed into a toxoid by formalin.[57] The discovery came about when the containers in which the batches of diphtheria toxin were kept were cleaned with formalin (they were too large to be autoclaved). The residual formalin in the vats rendered the batch of toxin so weak that 1000 times the normal dose did not kill the guinea pigs. Although using this "toxoid" was certainly safer than using toxin, it could be administered only in conjunction with antitoxin. In that same year, Gaston Ramon developed a diphtheria toxoid that could be used on its own (i.e., without antitoxin) by adding formalin and incubating the mixture at 37°C for several weeks.[58]

Ramon and Christian Zoeller went on to use a tetanus toxoid developed in the same manner for the first human vaccinations against tetanus in 1926.[59,60]

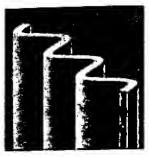
The vaccine against tuberculosis, Bacille Calmette-Guérin (BCG), was the first live vaccine for humans to be produced since Pasteur's rabies vaccine in 1885. Albert Calmette was a Pasteur protégé and founder of the Pasteur Institutes at Lille and in Indochina.[11] In 1906, Calmette and Camille Guérin started subculturing a strain of mycobacteria obtained from a bovine, which they perhaps thought was the tubercle bacillus. After 13 years of attenuation by 230 passages in beef bile, this strain eventually became the BCG strain. Clinical trials in children began in 1921, and the vaccine became available for human use in 1927.[11,61–65]

In 1931, E. W. Goodpasture introduced the use of the chorioallantoic membrane of the fertile hen's egg as a medium for growing viruses.[28,66] This technique represented a major advance, because until then human viruses could be grown only in animals such as ferrets and mice. Ferrets were

Chapter 8

General Immunization Practices

WILLIAM L. ATKINSON • LARRY K. PICKERING •
JOHN C. WATSON • GEORGES PETER



Recommendations for immunization practices are based on scientific knowledge of vaccine characteristics, the principles of immunization, the epidemiology of specific diseases, and host characteristics. In addition, the experience and judgment of public health officials and specialists in clinical and preventive medicine play a key role in developing recommendations that maximize the benefits and minimize the risks and costs associated with immunization. General guidelines for immunization practices are based on evidence and expert opinion of the benefits, costs, and risks of vaccinations as they apply to the current epidemiology of disease and use of vaccines in the United States. However, many of the principles are universal and are applicable to other countries where different public health infrastructures may exist.

Vaccine Storage and Handling

Vaccines must be properly shipped, stored, and handled to avoid loss of their biologic activities. Recommended storage and handling requirements for each vaccine are given in each manufacturer's product label.[1] Correct shipping, storage, and handling practices also are published in the recommendations of the major vaccine policy-making committees, such as the Advisory Committee on Immunization Practices (ACIP) of the United States Public Health Service, the Centers for Disease Control and Prevention and the American Academy of Pediatrics (AAP) (see Chapter 53).[2–5] Failure to adhere to these requirements can result in loss of vaccine potency, leading to an inadequate immune response in the vaccinee. Visible evidence of altered vaccine integrity may not be present. The manufacturer should be contacted when questions arise about the correct handling of a vaccine. New vaccines or new formulations of an existing vaccine may have different shipping, storage, and handling requirements. Table 8–1 gives recommended storage practices for the most commonly used vaccines in the United States.

Exposure to either higher or lower temperatures than recommended can inactivate a vaccine (see Table 8–1). For example, live virus vaccines such as oral poliovirus vaccine (OPV) and varicella are sensitive to temperatures above freezing and should be kept frozen until just before administration. Measles-mumps-rubella (MMR) vaccine and yellow fever vaccine should be kept frozen, although storage below 8°C (46°F) and below 5°C (41°F), respectively, is acceptable.[3,6] However, vaccines composed of purified antigens or inactivated microorganisms, such as hepatitis A, hepatitis B, *Haemophilus influenzae* type b (Hib), and influenza, can lose their potency if frozen and therefore should be kept at 2° to 8°C (36° to 46°F) and never frozen.[3,4] Diluents should not be frozen, and may be kept at room or refrigerator temperature.[3,4] Maintenance of a "cold chain" from vaccine production to use helps ensure vaccine potency at the time of administration. Temperature monitoring and control is important for storage and handling of all vaccines, particularly during transport and field use. Temperatures should be monitored regularly (at least twice a day), preferably using a thermometer that records current, maximum, and minimum temperatures. Whereas maintenance of cold and freezing temperatures is a problem in tropical climates, data suggest that inappropriate freezing of inactivated vaccines is a problem in maintaining vaccine stability in cold and temperate climates.[7] Kendal and associates[7] have suggested methods for packing and shipping vaccines based on tests conducted under representative conditions within the United States. Shipping containers should be sturdy and the correct size for the amount of vaccine to be shipped. Appropriate insulation (e.g., panels and boxes of polystyrene, isocyanurate, or polyurethane) and cold source (e.g., dry ice, gel packs, or bottles with frozen liquid) should be used to maintain the recommended temperature. Loose fillers do not provide reliable temperature insulation.

Vaccines should not be reconstituted until immediately before use. If not administered within the time interval

TABLE 8–7 ■ Vaccination During Pregnancy

Vaccine	Type	Indications for Vaccination During Pregnancy
	LIVE VIRUS	
Measles-mumps-rubella	Live, attenuated virus	Contraindicated
Poliomyelitis	Trivalent live, attenuated virus (oral poliovirus vaccine)	Persons at substantial risk of exposure to polio
Varicella	Live, attenuated virus	Contraindicated
Yellow fever	Live, attenuated virus	Contraindicated, except if exposure to yellow fever virus is unavoidable
	LIVE BACTERIAL	
Typhoid	Live, attenuated bacteria (Ty21a)	Should reflect actual risks of disease and probable benefits of vaccine
	INACTIVATED VIRUS	
Hepatitis A	Inactivated virus	Data on safety in pregnancy are not available; should weigh the theoretical risk of vaccination against the risk of disease
Hepatitis B	Recombinant-produced, purified hepatitis B surface antigen	Pregnancy is not a contraindication
Influenza	Inactivated type A and type B virus components	Recommended both for women who will be in the second or third trimester during influenza season and for patients with serious underlying disease; consult health authorities for current recommendations
Japanese encephalitis	Inactivated virus	Should reflect actual risks of disease and probable benefits of vaccine
Poliomyelitis	Inactivated virus (inactivated poliovirus vaccine)	Persons at substantial risk of exposure to polio
Rabies	Inactivated virus	Substantial risk of exposure
	INACTIVATED BACTERIAL	
Haemophilus influenzae type b conjugate	Polysaccharide-protein	Only for high-risk persons
Meningococcal	Polysaccharide	Only in unusual outbreak situations
Pneumococcal	Polysaccharide	Only for high-risk persons
Typhoid	Polysaccharide	Should reflect actual risks of disease and probable benefits of exposure
	TOXOIDS	
Tetanus-diphtheria	Combined tetanus-diphtheria toxoids, adult formulation (Td)	Lack of primary series, or no booster within last 10 yr (5 yr, if other than clean minor wounds)
	OTHER	
Immune globulins, pooled or hyperimmune	Immune globulin or specific globulin preparations	Exposure or anticipated exposure to measles, hepatitis A, hepatitis B, rabies, tetanus

pregnancy. No known risk exists for the fetus from passive immunization of pregnant women with immune globulin preparations.

Use of Live Vaccines

Live vaccines contain attenuated viruses or bacteria that multiply within the vaccine recipient. Because some of the diseases they prevent, such as rubella or varicella, are known to have teratogenic or other serious effects on the fetus, live virus vaccines usually are contraindicated during pregnancy.[5,231,239] All pregnant women should be evaluated for immunity to rubella.[79,258] Women susceptible to rubella should be vaccinated immediately after delivery.

Pregnancy should be avoided for 4 weeks after the receipt of parenteral live virus vaccines, by which time antibody production usually has occurred and vaccine-virus viremia is expected to have ceased.[79,236,259] Routine pregnancy testing of women of child-bearing age before administering a live virus vaccine is not recommended.[5,79] The ACIP recommends that the clinician should ask if a woman is pregnant or attempting to become pregnant, not administer live virus vaccines if a woman states that she is pregnant or attempting to become pregnant, explain the potential risk for the fetus to the woman who states that she is not pregnant, and then administer the indicated live virus vaccine.[5,79] Both OPV and yellow fever vaccine can be administered to pregnant women who are nonimmune and at substantial risk of imminent exposure to infection, such as from impending international travel.[5,231,260]